

REMARKS/ARGUMENTS

Claims 1-8 were previously cancelled and claim 9 is now cancelled.

Claims 10-18 remain in the application.

Claim Rejections under 35 USC § 103:

Claims 9-18 are rejected under 35 USC §103 as being unpatentable over either DE 44 08 011 of record, or DE 41 32 345 of record, or Arndt (Breast Cancer Research and Treatment, 1997) of record in combination with Jalonen (5,571,534), or in further combination with Grunicke (5,770,593).

Applicants respectfully traverse and these rejections will be considered together.

As pointed out by the Examiner, DE 44 08 011, DE 41 32 345, and Arndt teach liposomal compositions having the ability to inhibit the growth of tumor cells. However, none of these references teach the use of an additional antineoplastic agent such as tamoxifen in combination with the liposomal compositions. Jalonen discloses the use of tamoxifen in combination with lipids. And Grunicke discloses the use of tamoxifen in combination with a cis-platin antineoplastic compound.

Applicants respectfully submit that tamoxifen liposomes with the claimed composition show an unexpected increase in anti-tumor activity compared to the references of record. First, the inventors' previous work disclosed in DE 44 08 011 shows that the liposome compositions in and of themselves are active toward tumor reduction. The present invention relates to the combination of tamoxifen with similar liposome compositions which provides a surprising substantial improvement in tumor reduction. As illustrated in Table 1 of the application, while tumor reduction of 12% in mice was observed for the liposome compositions themselves, the combination of tamoxifen with the liposome compositions provides 37% tumor reduction in mice, more than three times the effect. This factor of improvement *in vivo* is an enormous effect which represents an unexpectedly advantageous property over the references of record. No such significant improvement is predicted or suggested by the references of record.

By comparison, Jalonen merely discloses that antiestrogens are poorly soluble in water and in order to improve their solubility they may be encapsulated in liposomes. However, Jalonen did not suggest or demonstrate any antitumor activity of the combination of liposomes with anti-estrogens. Thus, there is no motivation arising from any of DE 44 08 011, DE 41 32 345, Arndt, or Jalonen to combine liposomes with anti-estrogens. The Examiner must point to disclosure showing a reasonable expectation of success of such combination.

Further, Grunicke merely describes certain combinations of active pharmaceutical ingredients for tumor reduction, such as the combination of tamoxifen and a cis-platin. However, nowhere does Grunicke suggest the combination of tamoxifen and liposome compositions similar to the present invention for antineoplastic effects. Moreover, Grunicke only measured screening activities *in vitro* in a cell-based assay. There is no suggestion whatsoever that these results will be correlated to *in vivo* or clinical results. Thus, Grunicke does not suggest the present invention

and does not provide a reasonable expectation of success of achieving the inventors' surprising results.

In light of above evidence, Applicants respectfully request reconsideration and withdrawal of the rejections, since the claims are now in condition for allowance.

Conclusion:

Based on the foregoing amendments and remarks, favorable consideration and allowance of all of the claims now present in the application are respectfully requested.

Should the Examiner require or consider it advisable that the specification, claims and/or drawings be further amended or corrected in formal respects in order to place the case in condition for final allowance, then it is respectfully requested that such amendment or correction be carried out by Examiner's Amendment and the case passed to issue. Alternatively, should the Examiner feel that a personal discussion might be helpful in advancing this case to allowance, the Examiner is invited to telephone the undersigned.

The Commissioner is authorized to charge any required fees, including any extension and/or excess claim fees, any additional fees, or credit any overpayment, to Goodwin Procter LLP Deposit Account No. 06-0923.

Respectfully submitted for Applicants,


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